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CXCR4-TROPIC VIRUSES ARE COMMON AMONG ANTIRETROVIRAL TREATED PATIENTS WITH DETECTABLE VIREMIA AND ASSOCIATED WITH LOWER TREATMENT-MEDIATED CD4 GAINS

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Peter Hunt¹, J Martin¹, M Bates², W Huang², S Spudich¹, R Price¹, D Williamson³, E Sinclair³, R Hoh¹, and S Deeks¹

¹Univ of California, San Francisco, US; ²Monogram Biosci, South San Francisco, CA, US; and ³Gladstone Inst of Virology and Immunology, Univ of California, San Francisco, US

BACKGROUND: Among untreated HIV-infected individuals, CXCR4 (X4)-tropic viruses are uncommon except in advanced stages of immunodeficiency. However, little is known about the prevalence and immunologic consequences of X4 tropism in treated patients with detectable viremia.

METHODS: The chemokine receptor tropism of plasma viral isolates was determined by the HIV Entry Assay and compared between untreated and ART-treated, chronically infected patients sampled from 2 San Francisco cohorts. Differences between groups were adjusted for CCR5 Δ 32 genotype, nadir CD4+ T cell count, and duration of HIV infection. The association between tropism and naïve (CD45RA⁺CD62L⁺), activated (HLA-DR⁺CD38⁺), and non-activated memory CD4 counts was also assessed.

RESULTS: Both the 81 untreated patients and the 186 treated patients were similar as to median CD4 counts (258 vs 294 cells/mm³) and years since initial HIV diagnosis (13 vs 12 years), but untreated patients had lower median plasma HIV RNA levels (3.6 vs 4.0 log₁₀ copies/mL) and nadir CD4 counts (60 vs 203 cells/mm³). The treated patients had a median of 4 nucleoside reverse transcriptase inhibitor (NRTI)-associated and 2 major protease inhibitor (PI)-associated mutations. Of 186 treated patients, 75 (40%) harbored dual/mixed or X4-tropic viruses compared with only 12 of 81 (15%) untreated participants, $p < 0.001$. Among all participants, dual/mixed or X4 tropism was more common in those with lower current and nadir CD4 counts ($p < 0.001$ for both comparisons) and in those heterozygous for the CCR5 Δ 32 polymorphism ($p = 0.02$). Even after adjustment for nadir CD4 count, duration of HIV infection, and CCR5 Δ 32

genotype, treated patients had 4-fold greater odds of dual/mixed or X4 tropism than untreated patients, $p = 0.004$. Patients harboring dual/mixed or X4-tropic viruses had lower naïve ($p = 0.05$) and resting memory CD4 counts ($p = 0.02$) than those harboring R5-tropic viruses, but similar activated CD4 counts ($p = 0.27$). Furthermore, after adjustment for plasma HIV RNA levels, treated patients harboring dual/mixed or X4 tropic viruses were maintaining 78 fewer CD4⁺ T cells/mm³ above their pre-treatment nadir than those harboring R5-tropic viruses ($p = 0.002$).

CONCLUSIONS: Treated patients with partial viral suppression are more likely than untreated patients to harbor dual/mixed or X4-tropic viruses, independent of the extent of current or prior immunodeficiency. Dual/mixed or X4 tropism is also associated with fewer treatment-mediated CD4⁺ T cell gains, perhaps due to a greater ability to deplete resting memory and naïve CD4 cells.

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